

Abstract

The stochastic discrete space-time model of an immune response on tumor spreading in a two-dimensional square lattice has been developed. The immunity-tumor interactions are described at the cellular level and then transferred into the setting of cellular automata (CA). The multistate CA model for system, in which all states of lattice sites, composing of both immune and tumor cells populations, are the functions of the states of the 12 nearest neighbors. The CA model incorporates the essential features of the immunity-tumor system. Three regimes of neoplastic evolution including metastatic tumor growth and screen effect by inactive immune cells surrounding a tumor have been predicted.

KEYWORDS: cellular automata, immunology of tumor growth , fractals, physics computing, physiological models.

Cellular automaton model for immunology of tumor growth.

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1 Introduction

Practically all forms in nature are products of different kind of growth. Mathematical growth models play an important role in research and description of dynamics of various biological populations, which can demonstrate both chaotic and/or regular behavior. Interest in mathematical modeling in immunology of tumor growth arises from the ability of models to describe and predict neoplastic growth and immune response on this growth. In our paper, we have investigated the growth model with kinetic mechanism for the immune response (T- lymphocyte) on tumor spreading in 2D-space. The immunity-tumor interactions have been described at the cellular level and then transferred into the setting of cellular automata (CA) simulation. CA [1] are mathematical idealizations of biological system where space and time are discrete, and cell states take on the finite set of discrete values. CA exhibit a large variety of dynamical behaviors from fixed-point convergence and periodical motion to spatio-temporal chaos.

In numerous experiments, it has been shown that cells execute random walks in a culture, and after moving in a certain direction cells can migrate or turn in new direction randomly or in response on some intercellular interactions with tumor cells. We assume that immune cell can execute random walks in free space or move towards tumor cells. After the tumor cell division, both daughter cells occupy 2 nearest neighbor sites if they are empty. Here we deal with CA, which can have the set of discrete space, time, orientation of moving cell, and limited number of different parameters indicating activity, living time, etc. Because of its inherent computational efficiency, CA calculational method is successfully applied to predator-prey ecosystems [2], interfacial diffusion fronts [2] [3], traffic flow [4] [5], autowave splitting [6], quantum mechanics [7], lava flows [8], the proliferation dynamics [9], the outbreeding populations [10].

The purpose of the paper is to imitate tumor spreading in 2D-space using a CA calculational method and the rule-based programming style. We model the rules governing the tumor-immunity interaction in order to understand and

make clear how intercellular interactions, random collision, and cell moving affect the tumor colony growth.

The growth model presented here is more complicated than usual models in statistical mechanics because the cell colony configuration at a given time step is not independent from previous configurations but is correlated in a complicated way, i.e. tumor-immunity interaction is non-Markovian process. The computer program developed is rather suitable and its graphic availability will be helpful in developing the understanding in the field of immunology of tumor growth.

Let us begin with a brief definition of immune response and tumor growth on a regular square lattice.

2 The initial configuration and occupation rules.

Biological growth is determined by tumor cell division (immune cell doesn't divide), stimulated and spontaneous immune cell influx, and intercellular interactions. The model presented takes into account the immune elimination capacity, a , the growth rate of a tumor population with the parameter θ of competition for resources, the rate of immune cells inactivation, β , as a result of the immunity-tumor interaction, the accumulation of immune effector cells, c , in a region of a tumor (immunogenic tumor stimulates an influx of immune cells), is the spontaneous influx, j , of the active immune cells into the region of the tumor, and the rate of the immune cell elimination, γ , resulting from cell destruction or migration out of the localization area [11] [12]. The random distribution of immune cells and the tumor cell seed in the center of the square lattice are used to create the initial dynamical system configuration, and then is transferred into the setting of CA. It has been assumed that the tumor remains stationary while immune cells execute random walks in free space or move to any of the 4 adjacent sites, namely, north (N), east (E), south (S), and west (W) (Fig.1), if that sites are empty. Each immune cell has state values determined by the movement orientation, the time clock indicating the living time, and the indicator of activity (active or inactive). Each tumor cell has a state value indicating the time till division. To define the CA moving rules in a 2D-rectangular lattice, it is necessary to consider 12 nearest neighbor sites near cell, as shown in Fig.1.

The rules governing the behavior of the tumor-immunity system are implemented as the rewrite rules for all sites of the cellular automata lattice. It should be noted, that all growth rules are probabilistic, i.e. contain a random choice. Each time step increases the integer time clock value of the tumor or the immune cell by 1, unless the tumor cell division or the immune cell death occurs. In this case a new tumor cell occupies any empty nearest neighbor place, if it exists, or an immune cell is discarded from the immune cell population leaving an empty site, respectively. When the immune cell interacts a tumor cell occupying an adjacent site, it can eliminate a tumor cell with the probability a

Figure 1: Illustration of interaction range of a cell.

and occupies this site, or the immune cell is inactivated by a tumor cell with the probability b . In this case the immune cell remains in its site, but belongs to the inactive cell population. We also used the rules that prohibit more than one walker occupying a given site at a given time step. The immune cell moving to an adjacent empty site or to a site occupied by a tumor cell faced by another immune cell remains in its site if its living time is larger than the one of another immune cell. So, the first immune cell holds its orientation, but increases its time. Applying these update rules simultaneously to all the lattice sites of the system, we can simulate the tumor-immunity interaction in a 2D-space. The tumor growth can be stopped after n time steps or when tumor cells reach the lattice boundary.

3 Results.

After n growth rules applications the immunity-tumor system yields the tumor cluster and the distributions of active and inactive immune cells. Three regimes of the immune response and tumor dynamics have been determined. These are:

- normal wound healing (the total number of tumor cells tends to zero),
- uncontrolled (exponential) tumor growth,
- noise-like chaotic tumor-immunity behavior.

Figure 2: Tumor growth dynamics (N curve) and leukocyte dynamics (L curve).

The presented growth model shows that the immune response on 2D-space tumor spreading exhibits oscillatory fluctuations (see Fig.2 for the second regime), and that the normal wound healing, when the amount of tumor cells is equal to 0 after n time steps, has a probabilistic character. The probability of normal wound healing increases as the division time, d , is greater than the immune cell living time, but for a considerable amount of inactivated immune cells the increase in the living time leads to a screening effect by inactive immune cells surrounding tumor cell.

Figs.23 show the typical pattern of the uncontrolled tumor spreading when the immune response failed due to the low elimination capacity and the fast tumor growth, where $N(t)$ is the number of tumor cells and $L(t)$ is the number of leukocytes.

Fig.3 shows the spatial patterns of the tumor spreading at time step 100 on the 50×50 lattice. Active and inactive immune cells are indicated in gray (inactive cell - in light gray), tumor cells are in black, and the empty sites are in white. Starting from random immune cell configurations and the tumor seed in the center, the immunity-tumor system forms a cluster structure depending on the parameters of the model. The parameters chosen are: $a = 0.5, d = \gamma = 4, \beta = 0.3$, and the accumulation rate of immune cells is $c = 0.8$. The tumor growth model exhibits a new specific type of dynamical scaling which

Figure 3: Distribution of tumor cell and leukocytes.

is intimately related to the geometrical form. Geometrical properties of this tumor colony may be approximated as fractal [13] and its fractal dimension has been estimated is equal to 1.33006.

The third regime of the growth model presented shows drastic oscillatory fluctuations and exhibit noise-like chaotic behavior (Fig.4).

The parameters chosen are: $a = 0.82$, the time of division is equal 4, the immune living time γ is equal 6, $\beta = 0.3$, and the immune-cell accumulation rate c is 0.08. This regime has been analyzed by the Hurst's approach [13].

Fig.5 shows that the time series of the number of tumor cells $N(t)$ and also the number of leukocytes $L(t)$ follow the empirical law, $R/S = A\tau^H$, where rescale range $R(\tau)$ is

$$\mathbf{R}(\tau) = \max \sum_{u=1}^n N(u) - \overline{N} - \min \sum_{u=1}^n N(u) - \overline{N} \quad (1)$$

where \overline{N} is the mean of the series ($1 \leq n \leq \tau$), and the standard deviation of the cell number at the interval of observation, 20 to 500, $S(\tau)$ is

$$S(\tau) = \sqrt{\frac{1}{\tau} \sum_{u=1}^{\tau} (N(u) - \overline{N})^2} \quad (2)$$

The Hurst's exponent is defined from the slope of the asymptotic line, H , is 0.82 and A is 0.48 (Fig.5).

Figure 4: Number of tumor cells vs time.

Figure 5: Hurst's exponent vs number of observations.

As is seen, the curves $N(t)$ and $L(t)$ have the selfaffine character, and a fractal dimension of a trajectory as a curve can be estimated, $D_F = 2-H = 1.18$. The determined value of $H > 0.5$ indicates the strictly persistent character of the tumor growth with low noise level. The tumor growth persistency allows to predict statistically the amplitude and time of the tumor colony value at the future time intervals on the basis of already observed data.

4 Conclusions.

In this paper, we have developed the model that uses the cellular automata to imitate the process of the tumor-immunity interaction and presents simulation results carried out on 2-dimensional grid. Our model is computationally efficient and simulates movement, growth and interaction tumor and immune cells better than models using differential or difference equations. The immune response on tumor spreading in $2D$ -space exhibits oscillatory fluctuations and dependence on initial distribution, so that the normal wound healing has a probabilistic character. The probability of normal wound healing increases as the division time is greater then the immune cell living time, but in the case of considerable immune cell inactivation an increase in living time leads to the effect of screening by inactive immune cells surrounding tumor cell.

It has been found that the dynamics of the interacting populations shows self-organization and depends of the various experimental parameters and initial configurations. Three regimes of the immunity-tumor interactions have been determined. The results of simulation reveal a significant increase in the growth rates with increasing of average number of inactive immune cells, and decreasing of the active immune cell elimination capacity. Time series generated by the model follows the empirical Hursts law and demonstrates the strictly persistent character of the tumor growth with low noise level.

The computer program developed is rather suitable and its graphic availability is helpful in investigation of tumor growth immunology and for creation the control strategies in immune therapy.

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